Reference Type: Journal Article
Record Number: 371
Author: Hulthe, J.; Wiklund, O.; Hurt-Camejo, E.; Bondjers, G.
Year: 2001
Title: Antibodies to oxidized LDL in relation to carotid atherosclerosis, cell adhesion molecules, and phospholipase A(2)
Journal: Arterioscler Thromb Vasc Biol
Volume: 21
Issue: 2
Pages: 269-74.
Label: 21114232
Keywords: Antibodies/blood
Biological Markers
Carotid Arteries/anatomy & histology/immunology/ultrasonography
Carotid Artery Diseases/diagnosis/*immunology/ultrasonography
Cell Adhesion Molecules/blood
Female
Human
Immunoglobulin G/blood
Lipoproteins, LDL/*immunology
Male
Middle Age
Phospholipases A/blood
Support, Non-U.S. Gov't
Tunica Intima/anatomy & histology/immunology/ultrasonography
Abstract: -The role of the humoral immune response to oxidized low density lipoprotein (Ox-LDL) in atherogenesis is unclear and available studies are contradictory. The aims of the present study were (1) to compare antibody titers to modified LDL in a group of patients with hypercholesterolemia (n=102) with those in matched controls (n=102), (2) to analyze whether these titers were related to atherosclerosis development as measured by ultrasound, and (3) to analyze whether these titers were related to soluble cell adhesion molecules and secretory type II phospholipase A(2) in plasma. The results showed that male patients with hypercholesterolemia had lower immunoglobulin G (IgG) titers compared with those in healthy controls. In the control group, there was an inverse correlation between intima-media thickness of the carotid artery bulb and IgM titers against Ox-LDL and malondialdehyde- LDL (r=-0.35, P:=0.001; and r=-0.31, P:=0.003, respectively). In the patient group, however, only weak associations were seen. IgG titers were positively associated with soluble intercellular adhesion molecule- 1, soluble E-selectin, and secretory type II phospholipase A(2). Taken together, the results of this study support the concept that the humoral immune response against Ox-LDL may be protective in early atherosclerosis. The pattern, however, is complex, and the role of the immune response may differ in different patient groups as well as at different stages of the disease.

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URL: http://www.ncbi.nlm.nih.gov/cgi-bin/Entrez/referer?http://www.atvbaha.org/cgi/content/full/21/2/269

Reference Type: Journal Article
Record Number: 804
Author: Bhakdi, S.; Torzewski, M.; Klouche, M.; Hemmes, M.
Year: 1999
Title: Complement and atherogenesis: binding of CRP to degraded, nonoxidized LDL enhances complement activation
Journal: Arterioscler Thromb Vasc Biol
Volume: 19
Issue: 10
Pages: 2348-54.
Label: 99453164
Keywords: C-Reactive Protein/analysis/*metabolism/pharmacology
Calcium/metabolism
Complement 3/analysis/metabolism
Complement Activation/drug effects/*physiology
Complement Membrane Attack Complex/*metabolism
Coronary Arteriosclerosis/etiology/*metabolism
Coronary Vessels/chemistry/metabolism/pathology
Electrophoresis, Gel, Two-Dimensional
Human
Lipoproteins, LDL Cholesterol/analysis/*metabolism
Neuraminidase/pharmacology
Phospholipase C/pharmacology
Phosphorylcholine/pharmacology
Protein Binding/drug effects/physiology
Support, Non-U.S. Gov't
Trypsin/pharmacology
Abstract: Complement activation occurs in temporal correlation with the subendothelial deposition of LDL during early atherogenesis, and complement also plays a pathogenetic role in promoting lesion progression. Two lesion components have been identified that may be responsible for complement activation. First, enzymatic degradation of LDL generates a derivative that can spontaneously activate complement, and enzymatically degraded LDL (E-LDL) has been detected in the lesions. Second, C-reactive protein (CRP) colocalizes with complement C5b-9, as evidenced by immunohistological studies of early atherosclerotic lesions, so the possibility exists that this acute phase protein also fulfills a complement-activating function. Here, we report that addition of LDL and CRP to human serum did not result in significant C3 turnover. Addition of E-LDL provoked complement activation, which was markedly enhanced by CRP. Binding of CRP to E-LDL was demonstrated by sucrose flotation experiments. Binding was Ca(2+)- dependent and inhibitable by phosphorylcholine, and the complement- activating property of E-LDL was destroyed by treatment with phospholipase C. These results indicated that CRP binds to phosphorylcholine groups that become exposed in enzymatically degraded LDL

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particles. Immunohistological studies complemented these findings in showing that CRP colocalizes with E-LDL in early human atherosclerotic lesions. Thus enzymatic, nonoxidative modification of tissue-deposited LDL can be expected to confer CRP-binding capacity onto the molecule. The ensuing enhancement of complement activation may be relevant to the development and progression of the atherosclerotic lesion.
URL: http://www.ncbi.nlm.nih.gov/cgi-bin/Entrez/referer?http://www.atvbaha.org/cgi/content/abstract/19/10/2348

Reference Type: Journal Article
Record Number: 822
Author: Blake, G. J.; Dada, N.; Fox, J. C.; Manson, J. E.; Ridker, P. M.
Year: 2001
Title: A prospective evaluation of lipoprotein-associated phospholipase A(2) levels and the risk of future cardiovascular events in women
Journal: J Am Coll Cardiol
Volume: 38
Issue: 5
Pages: 1302-1306
Abstract: OBJECTIVES: We sought to determine prospectively whether lipoprotein-associated phospholipase A(2) (Lp-PLA(2)) was a predictor of future cardiovascular risk in women. BACKGROUND: Inflammatory markers may help predict cardiovascular risk. Lp-PLA(2) levels have recently been hypothesized to be an independent predictor of cardiovascular risk in hypercholesterolemic men. METHODS: We conducted a prospective, nested case-control study among 28,263 apparently healthy middle-aged women to assess the risk of death from coronary heart disease, non-fatal myocardial infarction, and stroke associated with baseline levels of Lp- PLA(2) over a mean follow-up of three years. RESULTS: In univariate analysis, mean levels of Lp-PLA(2) correlated strongly with low-density lipoprotein cholesterol ($r = 0.51$; $p = 0.0001$), were lower among women currently using hormone replacement therapy (mean 0.98 mg/l vs. 1.23 mg/l; $p = 0.0001$) and were significantly higher at baseline among cases ($n = 123$) than controls ($n = 123$) (mean 1.20 mg/l vs. 1.05 mg/l; $p = 0.016$). However, the predictive value of Lp-PLA(2) was markedly attenuated after adjustment for these and other cardiovascular risk factors. Specifically, the multivariate relative risks of future cardiovascular events for women in the lowest (referent) to highest quartiles of Lp-PLA(2) were 1.00, 0.75, 0.64 and 1.17, respectively (all p values non-significant). In contrast, the adjusted relative risks of future cardiovascular events for each increasing quartile of C- reactive protein (another marker of low-grade inflammation) were 1.00, 1.78, 2.02 and 4.66, respectively (p-value for trend = 0.002). Inclusion of Lp-PLA(2) levels did not significantly attenuate this latter observation. CONCLUSIONS: In contrast to prior data among hyperlipidemic men, the current data suggest that Lp-PLA(2) is not a strong predictor of future cardiovascular risk among unselected women.

Reference Type: Journal Article
Record Number: 824

Source: https://www.industrydocuments.ucsf.edu/docs/shvj0001

Author: Caslake, M. J.; Packard, C. J.; Suckling, K. E.; Holmes, S. D.; Chamberlain, P.; Macphee, C. H.
Year: 2000
Title: Lipoprotein-associated phospholipase A(2), platelet-activating factor acetylhydrolase: a potential new risk factor for coronary artery disease
Journal: Atherosclerosis
Volume: 150
Issue: 2
Pages: 413-419
Abstract: A specific and robust immunoassay for the lipoprotein-associated phospholipase A(2) (Lp-PLA(2)), platelet-activating factor acetylhydrolase, is described for the first time. The immunoassay was used to evaluate possible links between plasma Lp-PLA(2) levels and atherosclerosis risk amongst susceptible individuals. Such an investigation was important because Lp-PLA(2) participates in the oxidative modification of low density lipoprotein by cleaving oxidised phosphatidylcholines, generating lysophosphatidylcholine and oxidised free fatty acids. The majority of Lp-PLA(2) was found associated with LDL (approximately 80%) and, as expected, enzyme levels were significantly positively correlated to LDL cholesterol. Plasma Lp- PLA(2) levels were significantly elevated in patients with angiographically proven coronary artery disease (CAD) when compared with age-matched controls, even though LDL cholesterol levels did not differ significantly. Indeed, when included in a general linear model with LDL cholesterol and other risk factors, Lp-PLA(2) appeared to be an independent predictor of disease status. We propose, therefore, that plasma Lp-PLA(2) mass should be viewed as a potential novel risk factor for CAD that provides information related to but additional to traditional lipoprotein measurements.

Reference Type: Journal Article
Record Number: 828
Author: *Hakkinen, T.*; *Luoma, J. S.*; *Hiltunen, M. O.*; *Macphee, C. H.*; *Milliner, K. J.*; *Patel, L.*; *Rice, S. Q.*; *Tew, D. G.*; *Karkola, K.*; *Yla-Herttuala, S.*
Year: 1999
Title: Lipoprotein-associated phospholipase A(2), platelet-activating factor acetylhydrolase, is expressed by macrophages in human and rabbit atherosclerotic lesions
Journal: Arterioscler Thromb Vasc Biol
Volume: 19
Issue: 12
Pages: 2909-2917
Abstract: We studied the expression of lipoprotein-associated phospholipase A(2) (Lp-PLA(2)), an enzyme capable of hydrolyzing platelet-activating factor (PAF), PAF-like phospholipids, and polar-modified phosphatidylcholines, in human and rabbit atherosclerotic lesions. Oxidative modification of low-density lipoprotein, which plays an important role in atherogenesis, generates biologically active PAF-like modified phospholipid derivatives with polar fatty acid chains. PAF is known to have a potent proinflammatory activity and is inactivated by its hydrolysis. On the other hand, lysophosphatidylcholine and oxidized fatty acids released from oxidized low-density

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lipoprotein as a result of Lp-PLA(2) activity are thought to be involved in the progression of atherosclerosis. Using combined in situ hybridization and immunocytochemistry, we detected Lp-PLA(2) mRNA and protein in macrophages in both human and rabbit atherosclerotic lesions. Reverse transcriptase-polymerase chain reaction analysis indicated an increased expression of Lp-PLA(2) mRNA in human atherosclerotic lesions. In addition, approximately 6-fold higher Lp-PLA(2) activity was detected in atherosclerotic aortas of Watanabe heritable hyperlipidemic rabbits compared with normal aortas from control rabbits. It is concluded that (1) macrophages in both human and rabbit atherosclerotic lesions express Lp-PLA(2), which could cleave any oxidatively modified phosphatidylcholine present in the lesion area, and (2) modulation of Lp-PLA(2) activity could lead to antiatherogenic effects in the vessel wall.

Reference Type: Journal Article
Record Number: 831
Author: *Hurt-Camejo, E.*; *Camejo, G.*; *Peilot, H.*; *Oorni, K.*; *Kovanen, P.*
Year: 2001
Title: Phospholipase A(2) in vascular disease
Journal: Circ Res
Volume: 89
Issue: 4
Pages: 298-304
Abstract: Secretory phospholipase A(2) (PLA(2)) can be proatherogenic both in the circulation and in the arterial wall. In blood plasma, PLA(2) can modify the circulating lipoproteins and so induce formation of small dense LDL particles, which are associated with increased risk for cardiovascular disease. In the arterial wall, PLA(2) can hydrolyze lipoproteins. The PLA(2)-modified lipoproteins bind tightly to extracellular proteoglycans, which may lead to their enhanced retention in the arterial wall. The modified lipoproteins may also aggregate and fuse, which can lead to accumulation of their lipids within the extracellular matrix. The PLA(2)-modified particles are more susceptible to further modifications by other enzymes and agents and can be taken up by macrophages, leading to accumulation of intracellular lipids. In addition, lysophospholipids and free fatty acids, the hydrolysis products of PLA(2), promote atherogenesis. Thus, these lipid mediators can be carried, either by the PLA(2)-modified lipoproteins themselves or by albumin, into the arterial cells, which then undergo functional alterations. This may, in turn, lead to specific changes in the extracellular matrix, which increase the retention and accumulation of lipoproteins within the matrix. In the present article, we discuss the possible actions of PLA(2) enzymes, especially PLA(2)-IIA, in the arterial wall during atherogenesis.

Reference Type: Journal Article
Record Number: 842
Author: Tsimihodimos, V.; Karabina, S. A.; Tambaki, A. P.; Bairaktari, E.; Miltiadous, G.; Goudevenos, J. A.; Cariolou, M. A.; Chapman, M. J.; Tselepis, A. D.; Elisaf, M.
Year: 2002

Source: https://www.industrydocuments.ucsf.edu/docs/shvj0001

Title: Altered distribution of platelet-activating factor- acetylhydrolase activity between LDL and HDL as a function of the severity of hypercholesterolemia
Journal: J Lipid Res
Volume: 43
Issue: 2
Pages: 256-263
Abstract: Platelet-activating factor-acetylhydrolase (PAF-AH) is a lipoprotein-associated phospholipase A2 capable of hydrolyzing platelet-activating factor (PAF) and oxidatively modified phospholipids. We studied the plasma- and lipoprotein-associated PAF-AH activity in patients with primary hypercholesterolemia. Thirty-eight unrelated patients with heterozygous familial hypercholesterolemia (HeteroFH), five patients with homozygous FH (HomoFH), and 33 patients with primary non-FH hypercholesterolemia (NonFH) participated in the study. In all patient groups the plasma PAF-AH activity was significantly elevated compared with 33 normolipidemic controls, the HomoFH having the highest and the NonFH patients showing the lowest enzyme activity. Gradient ultracentrifugation studies showed that this increase is not only due to the elevation in the plasma LDL but also to the increase in the PAF- AH activity associated with each LDL subfraction, being more profound in the small-dense LDL-5. Unlike LDL, no difference in the HDL- associated PAF-AH activity was observed among all groups. Consequently, an altered distribution of enzyme activity among apolipoprotein B (apoB)- and apolipoprotein A-I (apoA-I)-containing lipoproteins is observed in hypercholesterolemic patients, resulting in a significant decrease in the ratio of the HDL-associated PAF-AH to the total plasma enzyme activity compared with controls. This reduction is proportional to the increase of the plasma LDL-cholesterol (LDL-C) levels and consequently to the severity of the hypercholesterolemia. Thus, the ratio of HDL-associated PAF-AH-total plasma enzyme activity may be useful as a potential marker of atherogenicity in subjects with primary hypercholesterolemia.

Reference Type: Journal Article
Record Number: 844
Author: Packard, C. J.; O'Reilly, D. S.; Caslake, M. J.; McMahon, A. D.; Ford, I.; Cooney, J.; Macphee, C. H.; Suckling, K. E.; Krishna, M.; Wilkinson, F. E.; Rumley, A.; Lowe, G. D.
Year: 2000
Title: Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group
Journal: N Engl J Med
Volume: 343
Pages: 1148-1155
Abstract: BACKGROUND: Chronic inflammation is believed to increase the risk of coronary events by making atherosclerotic plaques in coronary vessels prone to rupture. We examined blood constituents potentially affected by inflammation as predictors of risk in men with hypercholesterolemia who were enrolled in the West of Scotland Coronary Prevention Study, a trial that evaluated the value of pravastatin in the prevention of coronary events. METHODS: A total of 580 men who had had a coronary

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event (nonfatal myocardial infarction, death from coronary heart disease, or a revascularization procedure) were each matched for age and smoking status with 2 control subjects (total, 1160) from the same cohort who had not had a coronary event. Lipoprotein-associated phospholipase A2, C-reactive protein, and fibrinogen levels, and the white-cell count were measured at base line, along with other traditional risk factors. The association of these variables with the risk of coronary events was tested in regression models and by dividing the range of values according to quintiles. RESULTS: Levels of C- reactive protein, the white-cell count, and fibrinogen levels were strong predictors of the risk of coronary events; the risk in the highest quintile of the study cohort for each variable was approximately twice that in the lowest quintile. However, the association of these variables with risk was markedly attenuated when age, systolic blood pressure, and lipoprotein levels were included in multivariate models. Levels of lipoprotein-associated phospholipase A2 (platelet-activating factor acetylhydrolase), the expression of which is regulated by mediators of inflammation, had a strong, positive association with risk that was not confounded by other factors. It was associated with almost a doubling of the risk in the highest quintile as compared with the lowest quintile. CONCLUSIONS: Inflammatory markers are predictors of the risk of coronary events, but their predictive ability is attenuated by associations with other coronary risk factors. Elevated levels of lipoprotein-associated phospholipase A2 appear to be a strong risk factor for coronary heart disease, a finding that has implications for atherogenesis and the assessment of risk.

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